REMARKS

This Amendment is in response to the Office Action mailed March 12, 2008. Claims 27, 35 and 98-100 previously pending have been cancelled. In addition, the withdrawn claims have been cancelled. Accordingly, Claims 1-100 are now cancelled. New Claims 101-104 have been added. No new matter has been added. Reconsideration is respectfully requested.

Objections

In the Office Action, the examiner objects to the sequence listing filed on November 28, 2007. The examiner objects to field <213> as invalid for the sequences. The examiner also objects because a SEQ ID NO. is required for all amino acids sequences having four or more amino acids, such as the tables listed in Tables 1 and 2 at pages 18 and 19. The examiner has helpfully noted that amending the tables to include the SEQ ID NOS. would obviate the objection.

Accordingly, a substitute sequence listing has been submitted herein. The sequence listing includes a valid field <213> for the respective sequences. In addition, SEQ ID NO. 19 has been corrected to correspond to VEGF isoform 121 encoded by the DNA sequence specified in SEQ ID NO. 20 and resulting from the cloning procedures described in the application as filed. In addition, SEQ ID NO. 21 has been corrected to reflect the mutated version of the VEGF isoform 121 encoded by the DNA sequence specified in SEQ ID NO. 22 and resulting from the cloning procedures described in the application as originally filed. SEQ ID NO. 23 has been corrected to accurately reflect the sequence of the first three extracellular domains of VEGFR2 determined by the DNA sequence specified in SEQ ID NO. 24 and resulting from the cloning procedures described in the application as filed. SEQ ID NO. 25 has been corrected to accurately reflect the sequence determined by the DNA sequence specified in SEQ ID NO. 26 and resulting from the cloning procedures described in the application as filed. SEQ ID NO. 26 has been corrected to accurately reflect the transmembrane/cytoplasmatic fragment of VEGFR2 resulting from the cloning procedures

described in the application as originally filed utilizing the primers corresponding to SEQ ID NOS. 9 and 10 on the known 1-3 domains of KDR. SEQ ID NOS. 27, 28 and 29 have been deleted as being superfluous and the following sequences renumbered.

§112 Rejections

Claims 27 and 98 stand rejected under 35 U.S.C. §112, first paragraph as containing new matter. More specifically, the examiner asserts that the phrase "VEGF2 polypeptide fragments corresponding to the third extracellular domain" in Claim 27, parts ii) and iii) has no support in the claims and the specification as originally filed. The examiner also asserts that the phrase "its aminoterminal fragments" in Claim 27, part iii) and the phrase "p64K protein aminoterminal fragments thereof" in Claim 27, part v) has no support in the specification as originally filed.

Claims 27 and 98 have been cancelled. In addition, the new claims pending do not include the phrases objected to by the examiner. The new claims refer to specific polypeptide fragments identified by the SEQ ID NO. in the specification. Accordingly, these rejections are moot in view of the amendments to the claims.

Claims 27 and 98 also stand rejected under 35 U.S.C. §112, first paragraph as failing to satisfy the written description requirement. More specifically, the examiner asserts that the specification does not reasonably provide adequate written description of any p64K protein or its aminoterminal fragments. The examiner also asserts that the specification fails to disclose the structure associated with the function of any p64K protein other than Neisseria meningitides. Accordingly, the new claims submitted herein refer to the p64K protein of Neisseria meningitides.

Claim 35 stands rejected under 35 U.S.C. §112, second paragraph as being indefinite. More specifically, the examiner asserts that Claim 35 is unclear on whether the administering step is part of the claimed composition. The examiner states that it is unclear what is incorporated into Neisseria meningitides outer membrane derived VSSP.

Claim 35 has been cancelled herein. The newly submitted claims no longer include the "administering" step objected to.

Obviousness Rejections

Claims 27, 35 and 100 stand rejected under 35 U.S.C. §103(a) as being unpatentable over WO 99/45018 in view of Stacker et al. and Lu et al. The examiner also asserts that Claims 27, 98 and 99 stand rejected under 35 U.S.C. §103(a) as being unpatentable over WO 99/45018 in view of Siemeister and Lu et al.

The examiner asserts that WO 99/45018 teaches an immunogenic composition that includes VEGF or an antigenic fragment thereof and KDR/flk-1 (VEGFR2) or antigenic fragments thereof combined with a pharmaceutically acceptable adjuvant. The examiner concedes that WO 99/45018 does not teach the VEGF polypeptide mutated to prevent binding to its receptor or that the VEGFR2 corresponds to the first three extracellular domains.

The examiner relies upon Stacker et al. for the disclosure of various VEGF-A mutants that have lost binding capability to the VEGFR2. The examiner also relies upon Lu et al. for the disclosure of VEGFR2 polypeptide fragments such as monomeric KDR mutant containing only the first three N-terminal domains (KDR1-3). The examiner then concludes that it would therefore be obvious to one or ordinary skill in the art at the time of the invention to substitute VEGFA mutants for the VEGF fragment of WO 99/45018 and substitute KDR1-3 for the KDR/flk-1 of WO 99/45018.

Similarly, with regard to Claims 27, 98 and 99, the examiner asserts that it would be obvious to one of ordinarily skill in the art to substitute VEGF antigenic fragment and KDR/flk-1 (VEGFR2) fragment in the immunogenic composition of the WO 99/45018 publication for the $VEGF_{121}\Delta$ 1-17 mutant that fails to bind to its receptors as taught by Siemeister et al. and the VEGFR2 polypeptide fragment corresponding to the first three extracellular domains of VEGFR-2 or just the third domain of VEGFR2 as taught by Lu et al.

to form a new immunogenic for active immunization against angiogenesis associated antigens.

As stated above, Claims 1-100 are cancelled. New Claims 101-104 are pending. New Claims 101-104 are not obvious in view of the cited references because the references cited do not disclose all of the elements of new Claims 101-104.

As mentioned above, the examiner concedes that WO 99/45018 does not teach the VEGF polypeptide mutated to prevent binding to its receptor or that the VEGFR2 corresponds to the first three extracellular domains. The examiner then replies upon Stacker and Lu for these elements.

There is no suggestion in either Stacker or Lu for substituting the mutant VEGF disclosed in Stacker et al. and KDR 1-3 disclosed in Lu et al. for the peptides utilized in WO 99/45018. There is no reason why one skilled in the art would utilize the peptides disclosed in Stacker and Lu in an immunogenic composition as claimed.

The article by Stacker et al., where the authors report mutations of amino acids 83 to 89 of VEGF, describes the potential application of the VEGF mutants in the study of differential morphological changes of endothelial cells in response to mitogeneic or permeabilizing stimuli. The authors indicate that these aminoacids are required for VEGF-VEGFR2 interaction and consequent VEGF-mediated proliferation of HUVEC cells. The investigators do not offer any indication regarding the use of the described mutants as immunogens.

Lu et al. only describes the domain 3 of the VEGFR2. In addition, the article does not include immunization data, nor does it teach or suggest the use of the domain in combination with a VEGF polypeptide impaired for receptor activation in an immunogenic composition as claimed.

In addition, Siemeister defines residues in VEGF other than those known to interfere in the interaction with VEGFR2. Again, there is no reason for combining the VEGF isoform mutant disclosed in Siemeister et al. with a VEGF polypeptide impaired for receptor activation in an immunogenic composition as set forth in the claims.

Applicants note also that new Claims 101-104 include specific SEQ ID NOs for the VEGF polypeptide impaired for receptor activation and respective fragments thereof. Support for this element can be found throughout the specification, for example, at page 20, line 1 and in Table 1. Applicants assert that these VEGF peptides are not disclosed by the cited references.

Therefore, it would not be obvious from the cited references that an immune response could be elicited by using the claimed VEGF polypeptides impaired for receptor activation in combination with at least one of the VEGFR2 polypeptide fragments specifically identified in new Claims 101-104.

The Supreme Court has noted that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does*...because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (emphasis added); *see also id.* at 1740-41 (requiring a determination of "whether there was an apparent reason to combine the known elements *in the fashion claimed* by the patent at issue") (emphasis added).

With regard to the above-identified application, Applicants respectfully assert that there is an inadequate teaching in the cited references as to why one skilled in the art would combine the elements disclosed in the prior art the way the claimed new invention does.

Accordingly, Applicants respectfully submit that the application is now in proper form for allowance, which action is earnestly solicited. If resolution of any remaining issue is required prior to allowance of the application, it is respectfully requested that the Examiner contact Applicants' attorney at the telephone number provided below.

Respectfully submitted,

/james f. harrington/
James F. Harrington
Registration No.: 44,741
Attorney for Applicants

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
(516) 822-3550
JFH/jp
298797_1.DOC